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NEUROSCIENCE FOREFRONT REVIEW

Decisive role of Reelin signaling during early stages of Alzheimer`s Disease

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Abstract

Alzheimer`s disease (AD) is one of the largest unmet medical needs of our society. Around 25 million patients worldwide together with their families are still waiting for an effective treatment. We have recently initiated a re-evaluation of our knowledge of the molecular and cellular mechanisms underlying sporadic AD. Based on the existing literature, we have proposed a mechanistic explanation of how the late-onset form of the disease may evolve on the cellular level. Here, we expand this hypothesis by addressing the pathophysiological changes underlying the early and almost invariant appearance of the neurofibrillary tangles (NFTs), the only reliable correlate of the cognitive status, in distinct brain areas and their consistent "spread" along interconnected neurons as the disease advances. In this review we present and discuss novel evidence that the extracellular signaling protein Reelin, expressed along the olfactory and limbic pathways in the adult brain, might hold a key to understand the earliest steps of the disease, highlighting the olfactory pathway as the brain's Achilles heel involved in the initiation of the pathophysiology characteristic of late-onset AD.

Introduction

Alzheimer`s Disease (AD), a severe neurodegenerative condition with progressive cognitive decline, is characterized by the presence of two neuropathological hallmarks, neurofibrillary tangles (NFTs) and senile plaques (Castellani et al., 2010). The disease presents itself in two variants: (i) the familial form, accounting for a small percentage of all AD patients, that is induced by dominant mutations in the amyloid precursor protein (APP), presenilin-1 (PS1) or PS2 genes, and (ii) the aging-associated sporadic or late-onset form that is characterized by the early presence of inflammatory mediators both in plasma and in the brain (Holmes et al., 2009, Eikelenboom et al., 2011). Importantly, a major risk factor for both forms of the disease is the inheritance of the ApoE ε4 allele (Genin et al., 2011).

Despite the fact that AD imposes an enormous burden to the society and the health-care system, accounting for approximately 200 billion dollars of direct medical costs per year in the USA only (Association., 2012), a promising treatment is not yet at the horizon. We argued, recently, that a thorough re-examination of our knowledge of the pathophysiology characteristic of late-onset AD is a prerequisite for developing successful new therapies and presented evidence that sporadic AD develops as a consequence of chronic inflammatory conditions and associated cellular stress-induced axonopathy (Krstic and Knuesel, 2013). This model emphasizes that the amyloid-β plaques develop as a consequence of cytoskeletal impairments in the axons of the tangle-bearing neurons. However, in our model we have not addressed the striking observation that the formation of NFTs in AD brains appears to follow a very robust and consistent pattern along the olfactory and limbic pathways (Braak and Braak, 1991, Price and Morris, 1999).

To illuminate a molecular basis for this almost invariant NFT "spread" in AD, we first review the existing data on neuropathological changes and the vulnerability of the olfactory-limbic system, including the peripheral olfactory epithelium, early in the course of the disease. This is then followed by the integration of recent experimental findings addressing the role of the extracellular signaling protein Reelin that is selectively expressed along the affected circuits and shown to be a potent suppressor of Tau phosphorylation (Herz and Chen, 2006, Knuesel, 2010). Moreover, the decline in Reelin expression is not only strongly affected by aging and chronic inflammatory conditions in animals (Knuesel et al., 2009), but constitutes also a very early phenomenon of AD pathophysiology in humans (Herring et al., 2012a). Based on the presented evidence we propose that reduction of Reelin-mediated signaling in the olfactory and limbic system accelerates and aggravates the age-associated hyperphosphorylation of Tau (Braak et al., 2011). This in turn is expected to profoundly impair cytoskeletal stability and axonal integrity and would facilitate the formation of NFTs and senile plaques in affected neurons, thereby tipping the balance from healthy to pathological aging and cognitive deterioration (Krstic and Knuesel, 2013). This view also strongly supports the hypothesis of a pivotal role of olfactory bulb-associated neuroinflammation (Calderon-Garciduenas et al., 2008, Majde, 2010) in the initiation of the late-onset AD.

Olfactory-limbic pathways and AD

In contrast to amyloid-β deposition that does not allow the formulation of a coherent distribution scheme (Braak and Braak, 1991) nor a correlation to the cognitive state of the affected individuals (Bierer et al., 1995, Nelson et al., 2012), NFT formation shows a distinct propagation pattern with the disease progression (Braak and Braak, 1991, Price and Morris, 1999) and correlates well with the cognitive deterioration (Bierer et al., 1995, Nelson et al.,

2012). As highlighted by Braak and Braak, the olfactory and limbic pathways of the allocortex are among the first affected brain areas in AD (Fig. 1A,B): Braak stage I is characterized by NFT formation in the transentorhinal cortex, in layer I of the entorhinal cortex, as well as in the antero-dorsal nucleus of the thalamus. Braak stage II includes the presence of NFTs in the deeper layer V of the entorhinal cortex, the CA1 of the hippocampus, and in the amygdala and its projection area – the basal magnocellular complex. Braak stages III-VI are characterized by the accumulation of NFTs in association areas of the isocortex and the aggravation of the pathology in all areas already affected.

In agreement with these initial neuropathological changes along the olfactory-limbic pathway, olfactory dysfunction and its correlation with dementia severity has been well documented in patients with AD already in the late 1980`s (Warner et al., 1986, Doty et al., 1987). Recent advances in imaging techniques confirmed previously described postmortem changes by providing evidence for reductions in fMRI signal intensities in the primary olfactory cortex, hippocampus and insula that were significantly correlated with olfactory impairments and cognitive decline in AD patients (Wang et al., 2010). These findings are also in line with the consistent olfactory deficits during pre-clinical stages of AD (Peters et al., 2003, Djordjevic et al., 2008), that appear to be highly predictive for the conversion from mild cognitive impairment (MCI) to AD (Devanand et al., 2000). Importantly, MCI patients carrying the ApoE ε4 allele (Bacon et al., 1998), as well as cognitively normal elderly ε4-carriers (Murphy et al., 1998) showed significantly poorer odor identification than those without an inherited ε4 allele.

In addition to their accumulation in the primary olfactory cortex, NFTs and neuropil threads (NTs) are also present in the olfactory bulb of AD patients, as early as at Braak stage II (Kovacs et al., 1999). The severity of this initial Tau pathology in the olfactory bulb strongly

correlates with the Braak staging of the cortical changes and the presence of clinical dementia (Christen-Zaech et al., 2003, Attems et al., 2005). In contrast, the presence of amyloid plaques in olfactory bulb is detected only in advanced disease stages, namely Braak V –VI (Christen-Zaech et al., 2003, Attems et al., 2005). Importantly, ApoE ε4 carriers display higher tau pathology in the anterior olfactory nucleus (AON) in comparison to the ε4 negative individuals (Tsuboi et al., 2003). Finally, an MRI study demonstrated that pronounced olfactory bulb and fiber tract atrophy, a specific hallmark of AD (Mundinano et al., 2011), is present already very early in MCI patients (Thomann et al., 2009). Along the same line, it was shown that dystrophic neurites in the olfactory epithelium show high accumulations of paired helical filaments (PHFs; precursor elements of neurofibrillary tangles) and intracellular APP/Aβ in AD patients (Arnold et al., 2010). However, a time-course of these changes still needs to be determined.

The olfactory epithelium with its olfactory receptor neurons that project directly to the brain is in intimate contact with the external environment. Hence, this potential Achilles `heel of the central nervous system is equipped with effective neuroprotective strategies to fight pathogens (Mellert et al., 1992) and to quickly regenerate after mechanical or chemical injury by rebuilding the olfactory epithelium from stem cells (Beites et al., 2005). In addition, viruses and bacteria that manage to penetrate into the olfactory bulb are efficiently detained from spreading by surrounding microglia (Kalinke et al., 2011, Herbert et al., 2012). During the course of aging, however, accumulating injuries to the olfactory system, e.g. by viruses (Majde, 2010) or pollution (Calderon-Garciduenas et al., 2008), may induce excessive neuroinflammation and ultimately lead to well described deterioration of the olfactory system (Lazarini et al., 2012). It is highly conceivable that this in turn will induce pathological changes in relayed brain centers (Koliatsos et al., 2004, Hu et al., 2012). Interestingly,

cerebral ischemia or intracerebral injections of LPS potently activate microglia not only at the site of injury, but also in the olfactory bulb (Lalancette-Hebert et al., 2009). Moreover, systemic immune challenge using LPS induces the production of pro-inflammatory cytokines IL-1β and TNF-α in the olfactory bulb (Mori et al., 2005, Johnson et al., 2006). Taken together these observations provide a link between neuroinflammation-associated risk factors of AD, such as stroke, brain injury, arthritis, obesity etc (Krstic and Knuesel, 2013), and early deterioration of the olfactory system and its interconnected brain areas in patients with AD.

In the next chapters we will present and discuss evidence for a molecular link between the initial injury to the olfactory system and the formation of NFTs, which precede the progressive cognitive decline in AD.

Reelin expression within olfactory-limbic pathways

Reelin is an extracellular matrix signaling molecule that played a crucial role in the evolution of the cerebral cortex in mammals by regulating its layering during development (Tissir et al., 2002). Besides controlling the radial migration of cortical neurons, Reelin is also required for the differentiation and maturation of dendrites and dendritic spines (Forster et al., 2010, Frotscher, 2010). While its expression during brain development is largely restricted to Cajal-Retzius cells in the marginal zone, Reelin expression in the adult brain is confined to olfactory and limbic pathways (Fig. 1C), where it modulates spine dynamics and synaptic plasticity, as well as suppresses Tau hyperphosphorylation (Herz and Chen, 2006, Forster et al., 2010, Knuesel, 2010). As documented previously (Alcantara et al., 1998, Martinez-Cerdeno et al., 2002, Ramos-Moreno et al., 2006), Reelin is expressed by granule, mitral and tufted cells of the olfactory bulb. Its immunoreactivity can be further detected along the long projections of the latter two principal cell types: the lateral olfactory tract and olfactory tubercle, as well as

in the neuropil of their projection areas: anterior olfactory nucleus, amygdala, piriform and entorhinal cortex. Further, Reelin is produced by the pyramidal cells of the piriform and entorhinal cortex projecting to thalamus and hippocampus, respectively. In the hippocampus itself, Reelin expression is restricted to local interneurons (Alcantara et al., 1998, Koliatsos et al., 2004, Ramos-Moreno et al., 2006, Knuesel et al., 2009). Finally, Reelin is also expressed in the corticomedial amygdaloid nuclei and the paraventricular nuclei of the thalamus. Interestingly in primates, but not in rodents, Reelin continues to be expressed in the isocortical layers I and II and by interneurons throughout the neocortex (Alcantara et al., 1998, Martinez-Cerdeno et al., 2002, Ramos-Moreno et al., 2006) where the pathology appears only in advanced stages of the AD (Braak and Braak, 1991).

Taken together, Reelin-expressing cells and their projections are positioned along the areas that are the first to be affected in AD by NFT pathology (Fig. 1B). In line with the olfactory deficits and diminished Reelin expression representing an early feature of AD in humans, heterozygous *reeler* mice also display deficits in olfactory learning (Larson et al., 2003). Importantly, acute damage to the olfactory epithelium results in rapid down-regulation of Reelin expression in the olfactory bulb (Okuyama-Yamamoto et al., 2005). During regeneration of the epithelium, Reelin-producing cells regain their expression capacity. However, repeated damage to the olfactory epithelium may promote long-term reductions in Reelin-mediated signaling in the olfactory system. This further suggests that the reduction in Reelin levels may constitute a molecular link between environmental and/or inflammatory injury to the olfactory pathway and the development of AD-associated changes early in the disease. In the following chapter we will review the experimental evidence that collectively support such a view (Fig. 2).

Dysfunctional Reelin signaling and its role in AD etiology

Reelin exerts its function by inducing the clustering of the apolipoprotein E receptor 2 (ApoER2) and the very low density lipoprotein receptor (VLDLR) (Hiesberger et al., 1999, Strasser et al., 2004). This in turn induces phosphorylation of the adaptor protein Disabled-1 (Dab-1) (Hiesberger et al., 1999), a process that activates cytosolic kinase pathways involving (i) SRC family tyrosine kinases (SFKs), leading to phosphorylation of NMDAR subunit NR2 on the postsynaptic membrane and the concomitant potentiation of NMDAR-mediated Ca^{2+} influx (Chen et al., 2005), and (ii) the activation of Phosphatidylinositol-3-kinase (PI3K) and protein kinase B (Akt/PKB) leading to inhibition of GSK3β (Beffert et al., 2002) and concomitant suppression of Tau hyperphosphorylation (Ohkubo et al., 2003), which is a key step in the formation of neurofibrillary tangles (Augustinack et al., 2002). The activaton of the Reelin pathway involving Dab-1, SFKs and PI3K also results in LIM1 kinase activation with a concomitant increase in n-cofilin phosphorylation, a signaling mechanism engaged in the leading processes of migrating neurons to stabilize the actin cytoskeleton (Chai et al., 2009). The Reelin-mediated effects on cytoskeletal dynamics may likely involve differential receptor activation through different binding domains of Reelin and/or Reelin proteolytic fragments (Jossin et al., 2004, Duit et al., 2010) and presumably persist in adult synapses (Frotscher, 2010). Interestingly, tissue plasminogen activator, shown to be induced by and involved in removal of Aβ aggregates (Tucker et al., 2000), cleaves Reelin at its C-terminal end (Krstic et al., 2012b) and by that modulate its binding to ApoER2 (Nakano et al., 2007). However, the biological significance of the proteolytic processing of Reelin might be more complex (Jossin et al., 2007, Chameau et al., 2009), and likely involves more downstream effects than only reducing binding of Reelin to its receptors, as previously proposed (Kohno et al., 2009).

Besides the modulation of NMDA receptor-dependent synaptic plasticity (Chen et al., 2005), it has recently been shown that Reelin also rescues amyloid beta (Aβ)-induced suppression of long term potentiation (LTP) in the hippocampus (Durakoglugil et al., 2009). Importantly, the ApoE ε4 isoform potently competes with Reelin for binding to its receptors (D'Arcangelo et al., 1999). Once bound to ApoER2, ε4 induces its degradation and concomitant sequestering of AMPA and NMDA receptors in intracellular compartments (Chen et al., 2010). As a consequence, ApoE ε4 and to a lesser extent ε3 but not ε2, reduces Reelin-mediated NMDA receptor phosphorylation/activity and synaptic availability (Chen et al., 2010). Hence the potent inhibition of LTP by $A\beta_{1-42}$ in an ApoE ε4 background (Trommer et al., 2005) can be explained by Reelin being outcompeted by ApoE ε4 to activate its downstream signaling and antagonizes Aβ. This is in line with the impaired LTP and cognitive performance seen in Reelin heterozygous knock-out mice (Krueger et al., 2006, Qiu et al., 2006), likely representing a consequence of altered NMDA receptor function in these mice (van den Buuse et al., 2012). In agreement, both Reelin heterozygous knock-out (Ohkubo et al., 2003) and ApoE ε4 knock-in mice (Kobayashi et al., 2003, Harris et al., 2004) show increased levels of Tau phosphorylation.

Reelin also modulates the endogenous role of APP, by promoting its surface localization either by enhancing the intracellular interaction of Dab-1 with both ApoER2 and APP (Hoe et al., 2006) or by decreasing APP endocytosis through direct binding to the N-terminal domain of APP (Hoe et al., 2009). It is conceivable that the Reelin-APP interaction is required to promote α-cleavage of APP (Parvathy et al., 1999) and neurite outgrowth (Hoe et al., 2009). In agreement with these *in vitro* findings, genetically reduced Reelin levels in $APP_{swe,arc}$ mice increased the production of Aβ peptide and significantly aggravated the plaque pathology (Kocherhans et al., 2010). Moreover, Reelin reduction in these mice, expressing endogenous

mouse Tau protein, induced the formation of PHF-like accumulations in the vicinity of the plaques (Kocherhans et al., 2010).

Besides its modulation of APP functions through ApoER2-mediated signaling, it was recently shown that Reelin also regulates microtubule assembly (Meseke et al., 2013) and promotes Cdc42-controlled transport of trans-Golgi-network-derived vesicles and increases growth cone motility, axonal branching and filopodia formation (Leemhuis et al., 2010). These findings highlight the context-dependent modulation of the actin and microtubule cytoskeleton through the Reelin-dependent signaling pathway in the developing brain (Forster et al., 2010, Zhao and Frotscher, 2010). It is equally conceivable that Reelin is required in the adult olfactory-limbic system to maintain a neuronal activity-dependent balance between plasticity and stability (Frotscher, 2010). Consequently, any impairments or loss of proper Reelin-mediated signaling is not only expected to destabilize interneuronal connections but also to prevent axonal sprouting and repair of damaged neurons in aging and AD (Krstic and Knuesel, 2013). In support of such a view is the observation that upon neuronal injury, Reelin expression is up regulated in Schwann cells (Panteri et al., 2006) and that Reelin knock-out mice show impaired peripheral nerve regeneration (Lorenzetto et al., 2008). It would be highly relevant, therefore, to check in the adult brain if oligodendrocytes, which express Reelin in vitro (Siebert and Osterhout, 2011), show increased Reelin expression upon axonal injury in the CNS. In addition, since hyperphosphorylated filamentous Tau can inhibit kinesin-based fast axonal transport (Kanaan et al., 2011), Reelin – via GSK3β kinase-mediated suppression of Tau hyperphosphorylation - may also support axonal transport integrity.

Importantly, we were recently able to demonstrate that a viral-like prenatal immune challenge predisposes the offspring to develop an AD-like phenotype, which is induced if the challenge

is repeated for a second time during adulthood (Krstic et al., 2012a). In these prenatally challenged mice, the loss of Reelin expressing cells (Meyer et al., 2008, Knuesel et al., 2009) coincided with an increase in APP production and cleavage, Tau hyperphosphorylation and missorting, as well as cognitive deficits (Krstic et al., 2012a). This is in agreement with the observations of cognitive decline in aged rats correlating with reduced Reelin expression in the entorhinal cortex (Stranahan et al., 2011a), recently confirmed by the findings of impaired spatial memory following experimental interference with Reelin signaling in the same area (Stranahan et al., 2011b). Moreover, behavioral and memory deficits are also observed after Reelin knock-down in the prefrontal cortex in adult rats (Brosda et al., 2011). The important role of Reelin in modulating synaptic functions has also been highlighted by the enhancing effect of intraventricular infusions of recombinant Reelin on cognitive performance, synaptic plasticity, and dendritic spine density in wild-type (Rogers et al., 2011) and Reelin heterozygous mice (Rogers et al., 2012). Interestingly, also exercise during pregnancy induces Reelin expression in offspring and mitigates plaque pathology in AD-mice (Herring et al., 2012b). It is also worth mentioning that Reelin plays a fundamental role in adult hippocampal neurogenesis, as recently shown by the Soriano group (Teixeira et al., 2012).

Intriguingly, Reelin was shown to accumulate in the projection areas of Reelin expressing cells in an age-dependent manner, a phenomenon observed in various species including primates (Knuesel et al., 2009). 3D electron microscopy in mice revealed that these protein accumulations are of intracellular origin (Doehner et al., 2012), strikingly resembling 3D reconstruction of the axonal diverticula in aged rhesus monkeys (Fiala et al., 2007). These bud-off granules are engulfed by surrounding glia (Knuesel et al., 2009, Madhusudan et al., 2009, Doehner et al., 2012), and were shown to be positive for various intracellular proteins including APP/Aβ and Tau (Doehner et al., 2010). In AD-transgenic and in prenatally

challenged wild-type mice, the number and size of these granules is increased and are enriched with degenerative mitochondria and other organelles (Knuesel et al., 2009, Doehner et al., 2012). Hence we proposed that these axonal "bud-offs" are indicative of a mechanism by which long projection neurons may extrude intracellular misfolded or aberrantly cleaved proteins, as well as degenerative organelles (Doehner et al., 2012), and through this enable undisrupted axonal transport and proper signal transduction (Krstic and Knuesel, 2013).

Finally, in humans both loss of Reelin expressing cells in the entorhinal cortex (Baloyannis, 2005, Chin et al., 2007) and drastically reduced levels of Reelin protein in the hippocampus, entorhinal and frontal cortex (Herring et al., 2012a) are prominent immunohistochemical features seen already in early-stages of AD. Interestingly, Reelin mRNA levels in the frontal cortex are up-regulated in later stages of AD (Botella-Lopez et al., 2006, Botella-Lopez et al., 2010), reflecting either a potentially compensatory mechanism or an effect of advanced disease processes. Unfortunately, as a likely consequence of the high inter-subject variability, the relative concentrations of Reelin and its proteolytic fragments in brain and CSF of AD patients and non-demented controls are inconclusive (Ignatova et al., 2004, Botella-Lopez et al., 2006), Notter and Knuesel, unpublished observations). Finally, a recent genome-wide association (GWA) study identified a highly significant correlation between single-nucleotide polymorphisms (SNPs) in the Reelin locus and protection against dementia in elderly with high NFT load in AD-vulnerable brain areas (Kramer et al., 2011). Moreover, Seripa and colleagues identified additional SNPs in the Reelin locus that were significantly associated with AD pathogenesis in women (Seripa et al., 2008), in agreement with the study showing that women have a higher risk for AD than men primarily related to the higher density of NFTs (Barnes et al., 2005). Since the identified SNPs are located mainly in CpG islands within the Reelin promoter (Chen et al., 2002), shown to undergo epigenetic modifications as

a part of regulatory mechanism of LTP (Levenson et al., 2008, Sui et al., 2012), it would be of highest relevance to further confirm (Kramer et al., 2011) and to check if these SNPs (Seripa et al., 2008) are correlated with a significant increase or decrease of Reelin levels, respectively. In line with Reelin's role in suppressing NFT formation, it is important to mention that elderly people with high AD pathology but no dementia, the so-called high pathology controls (Kramer et al., 2011, Krstic and Knuesel, 2013) differ from AD patients in the amount of NFT load in the frontal cortex (Maarouf et al., 2011).

An integrated view on AD initiation

Based on the analysis of postmortem human brains in the age range of 1–100 years, Heiko Braak and colleagues recently reported that Tau-related neuronal changes appear first in the locus coeruleus (Braak et al., 2011), a crucial brain stem nucleus implicated in stress response regulation(Valentino and Van Bockstaele, 2008). The following area to be affected with increasing age is the transentorhinal cortex with its axonal projections from Reelin-expressing cells located in the olfactory bulb (Fig. 1C) Here (Fig. 2), we propose that reduction of Reelin (Chin et al., 2007, Herring et al., 2012a), as a consequence of cumulative environmental injuries to the olfactory pathway (Okuyama-Yamamoto et al., 2005) or injury/disease/infection-induced chronic inflammation (Knuesel et al., 2009, Krstic and Knuesel, 2013), accelerates the age-dependent phosphorylation of Tau and instability of interneuronal connections. This will in turn result in a more pronounced synaptic loss and wide-spread formation of NFTs, a correlate of disease progression and dementia severity in patients with AD. Further, reduced Reelin-mediated signaling will lead to impairments in NMDA receptor modulation that might initially affect olfactory information processing, followed by hippocampus-dependent cognitive dysfunctions. In parallel, chronic

neuroinflammatory processes presumably provokes axonal stress in long projection neurons, leading to the formation of amyloid plaques and neurofibrillary tangles in cortical association areas, and might, in addition, impair the innate immune system of the brain to adequately support the vulnerable neurons. In addition, ApoE ε4, a major risk factor for AD, potently competes with Reelin and affects its downstream signaling and function. This view positions Reelin and its signaling members in the aging brain as a protective factor against cognitive decline. Accordingly, the reduction in Reelin signaling may shift the balance from healthy to pathological aging. Finally, targeting neuroinflammatory processes to treat AD (Krstic and Knuesel, 2013) might only be effective during prodromal stages, whereas later anti-inflammatory interventions may even be detrimental (Breitner et al., 2011). Hence, restoring Reelin expression or activation of Reelin-mediated signaling might be worth considering as a possible alternative therapeutic strategy in MCI patients and later stages of AD.

Conclusion

The distinct pathology in the limbic-olfactory brain areas and its consistent progression along interconnected neurons as the disease advances has recently received much attention. Here, we have highlighted the importance of a distinct neurodevelopmental program that is instrumental in the adult brain to modulate synaptic functions and maintain neuronal integrity. We argue that inflammation/injury-induced dysfunctions of the Reelin-signaling underlie the apparent “spread” of the neuropathology across brain networks in patients diagnosed with AD.

Figure Legends

Figure 1. Reelin is expressed along the pathways affected by NFTs in early AD. (**A**) Schematic drawing of a human brain showing the appearance of senile plaques (stars) and neurofibrillary tangles (NFT, triangles) in various stages of AD (Braak stages A-C/I-VI). Blue and green areas depict the areas affected by the pathology in the preceding stage (as indicated with the colored star and triangles). (**B**) Olfactory and limbic pathways are the first to be affected by the NFT pathology in AD. Schematic drawing of a rat brain showing olfactory/limbic connections is adapted from (Canavan et al., 2011). Abbreviations: OE, olfactory epithelium; OB, olfactory bulb; aOB, accessory olfactory bulb; AON – anterior olfactory nucleus; OT, olfactory tubercle; PIC, piriform cortex; EC, entorhinal cortex; LA/MA, lateral/medial amygdala; HC, hippocampus; HTH, hypothalamus; TH, thalamus. Areas affected with NFT pathology in early Braak stages I and II (gray) and later Braak stages III and IV (striped). (**C**) Reelin expression along the olfactory and limbic pathways. Abbreviations: gc, granule cells; mc, mitral cells; tc, tufted cells; pyr, pyramidal neurons; int, GABAergic interneurons; can, corticomedial amygdaloid nuclei; pn, paraventricular nuclei. Reelin immunoreactivity in the neuropil (blue areas).

Figure 2. Reelin and its role in AD neuropathology. Through its modulatory role on Tau phosphorylation as well as maintenance of synaptic integrity and plasticity (long-term potentiation, LTP), Reelin supports proper cognitive functions in the aging brain. This is likely achieved by a predominant suppressing effect on aging-associated cytoskeletal impairments that lead to axonal transport deficits, destabilization of synaptic contacts, and the formation of neurofibrillary tangles. Neuroinflammatory stimuli and environmental injuries to the olfactory epithelium would impair the neuroprotective functions of Reelin, increase the

levels of APP, and induce axonopathy that likely precedes the formation of plaques and tangles. Importantly, their impact on Reelin-mediated signaling is aggravated in an ApoEε4-dependent manner. Green color indicates protective effects; red color represents detrimental processes.

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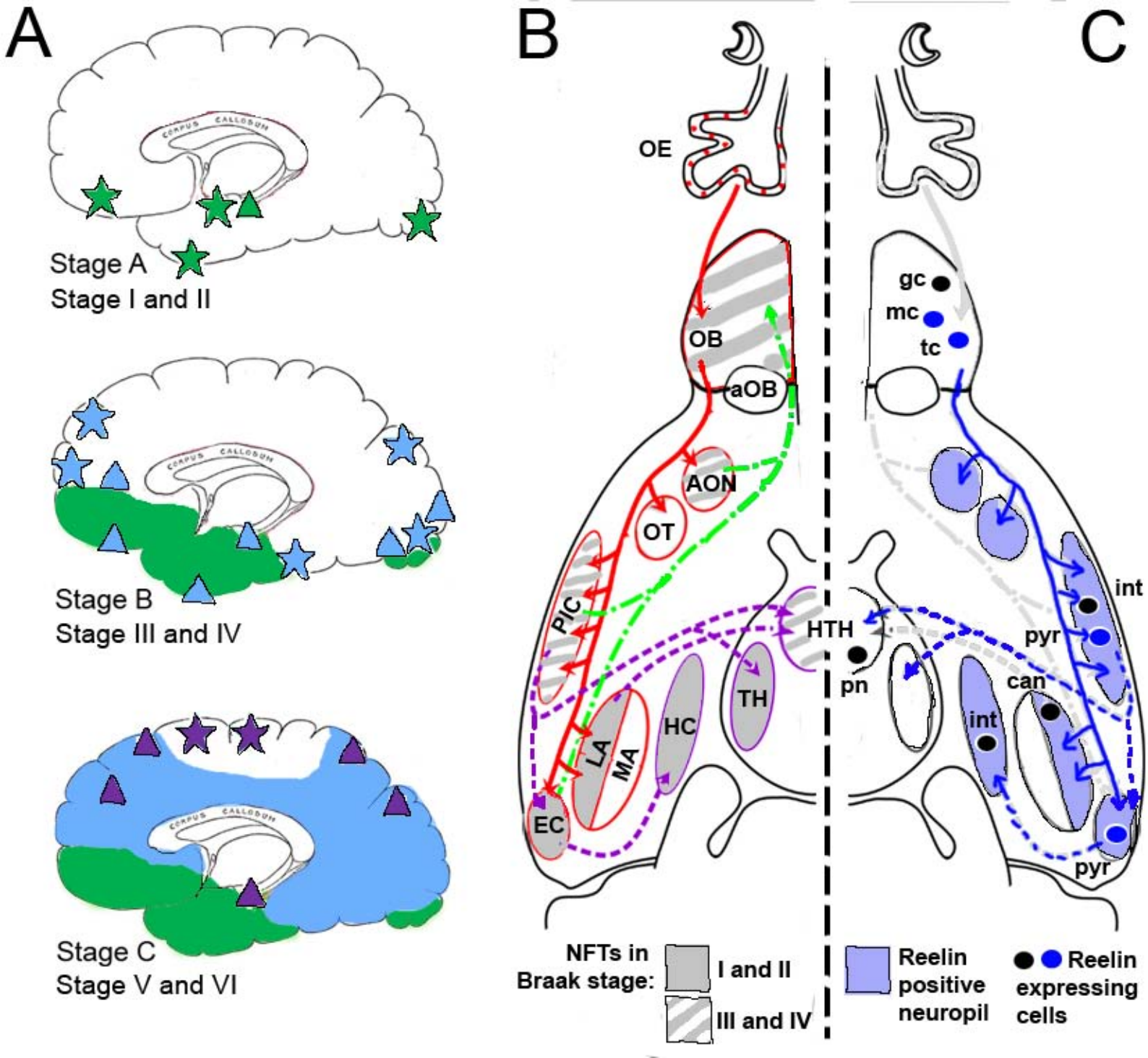
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NFTs in Braak stage:
I and II
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Reelin positive neuropil
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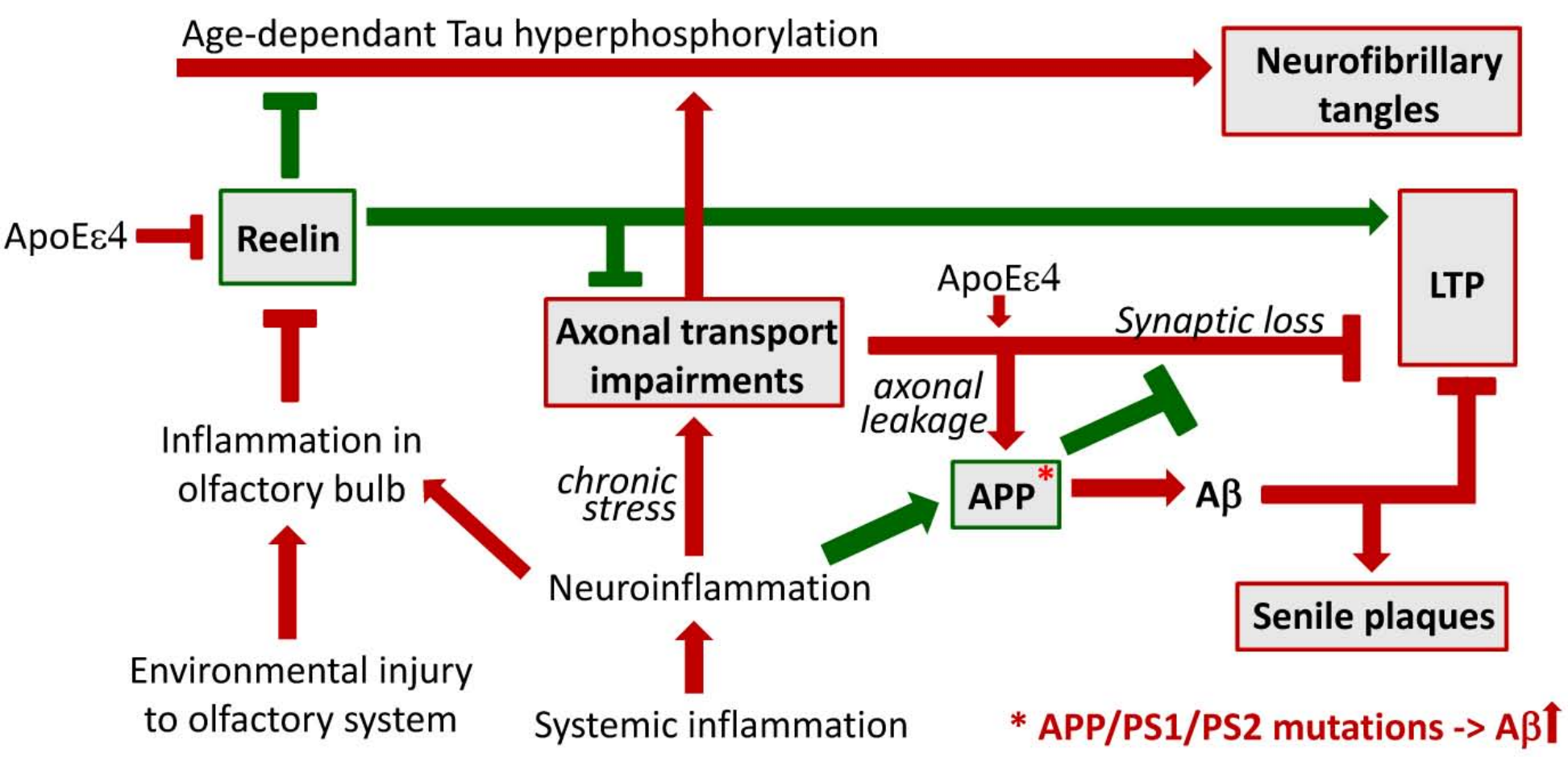
Age-dependant Tau hyperphosphorylation
Neurofibrillary tangles
ApoEε4
Reelin
LTP
Axonal transport impairments
ApoEε4
Synaptic loss
axonal leakage
Inflammation in olfactory bulb
chronic stress
APP*
Aβ
Neuroinflammation
Senile plaques
Environmental injury to olfactory system
Systemic inflammation
* APP/PS1/PS2 mutations -> Aβ↑

Figure 2